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ORIGINAL ARTICLE

# Characteristics of interstitial lung disease in SS-A positive/Jo-1 positive inflammatory myopathy patients

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**Abstract** The strongest predictive factor for the development of interstitial lung disease (ILD) in myositis (IIM) patients is the presence of different antisynthetase antibodies. The aim of this study was to compare the clinical characteristics, radiological findings and therapeutic response between the anti-SS-A positive and negative antisynthetase syndrome (ASS) patients. A prospective study of 315 IIM patients was conducted including 27 anti-Jo-1 positive ASS patients. Mean disease duration was 46.6 (range 4–198) months. All patients fulfilled the classification criteria for IIM. All patients underwent chest radiography, pulmonary function tests and HRCT at he time of diagnosis and 6 months after the immunosuppressive therapy. Routine laboratory tests, RF, ANA, anti-ENA, anti-SS-A, anti-histidyl-transfer RNA antibody (Jo-1) measurements were performed in all patients. ILD was found to be present in 70.4% of ASS patients. The anti-SS-A negative ASS group had a more frequent association with alveolitis and responded well to immunosuppressive therapy ($p < 0.05$). HRCT scan showed more fibrosis in the SS-A positive group. 15.8% of patients died due to pulmonary or cardiac complications. In conclusion, coexistence of anti-SS-A and anti-Jo-1 antibody may be a good predictor for a more coarse and severe ILD in IIM patients who require a more aggressive approach in therapy.

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**Abbreviations**

| | |
|---|---|
| ACR | American College of Rheumatology |
| ANA | Antinuclear antibodies |
| ASS | Antisynthetase syndrome |
| BOOP | Bronchiolitis obliterans and organizing pneumonia |
| CK | Creatinin kinase |
| CRP | C-Reactive protein |
| DAD | Diffuse alveolar damage |
| DLCO | Carbon monoxide diffusion capacity |
| ENA | Extractable nuclear antigen |
| FEV1% | Forced expiratory volume in 1 s |
| FVC | Functional vital capacity |
| HRCT | High-resolution computer tomography |
| IF | Immunofluorescence |
| IIM | Idiopathic inflammatory myopathy |
| ILD | Interstitial lung disease |
| IPF | Idiopathic pulmonary fibrosis |
| Jo-1 | Histidyl-transfer RNA synthetase |
| LDH | Lactate-dehydrogenase |
| NSIP | Non-specific interstitial pneumonia |
| MSA | Myositis-specific antibody |
| OM | Overlap myositis |
| PFT | Pulmonary function tests |

| | |
|---|---|
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| RNP | Ribonucleoprotein |
| SD | Standard deviation |
| SSc | Scleroderma |
| Sm | Smith antigen |
| tRNA | Transfer ribonucleic acid |
| UIP | Usual interstitial pneumonia |

## Introduction

Idiopathic inflammatory myopathy (IIM) is a systemic inflammatory disease of muscles with no definite origin, and is characterized by proximal muscle weakness, elevated serum necroenzymes, characteristic electromyography findings and lymphocytic infiltration in the muscle tissue. In the case of dermatomyositis, characteristic skin manifestations (heliotrop rash, Gottron papula) are also present [1]. Pulmonary involvement includes respiratory muscle weakness, aspiration pneumonia, infection and drug-induced pneumonia as well as the characteristic immune-mediated alveolitis [2]. The latter is found in a subgroup of myositis patients with antisynthetase syndrome (ASS) which is characterized by the presence of Raynaud phenomenon, polyarthritis, mechanic's hand, interstitial lung disease (ILD) and presence of different anti-aminoacyl-transfer ribonucleic acid (tRNA) synthetase antibodies in their sera [1].

The strongest predictive factor for developing ILD in myositis patients is the presence of different anti-aminoacyl-tRNA synthetase antibodies [3]. Anti-Jo-1 antibody can be found in 10–40% of patients with polymyositis (PM), 2–10% in dermatomyositis (DM) and 3–8% in overlap myositis [1, 4]. Other anti-aminoacyl-tRNA synthetases are present in 1–3% of patients with IIM. Prevalence of ILD in IIM has been reported to be 23.1–65% and it is the major cause of death [5]. The reported frequency of ILD is more than 70% in the Jo-1 positive patients [1, 4]. IIM patients with ILD can be categorized into three different pattern groups based on the disease's initial presentation: a group with an acute onset of symptoms, another with slowly progressive pattern and the third with asymptomatic pattern (those without pulmonary symptoms but abnormal chest radiographs and pulmonary function tests) [6]. According to the classification of the American Thoracic Society and European Respiratory Society of interstitial pneumonia, several patterns can be revealed in IIM, including bronchiolitis obliterans and organizing pneumonia (BOOP), diffuse alveolar damage (DAD), non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) [4]. Poor prognostic factors are the following: Hamman-Rich like pattern, low CK level, low DLCO, neutrophil bronchoalveolar lavage (BAL) fluid, lung histology of DAD or UIP [6].

Response to corticosteroids depends on the degree of inflammation or fibrosis. BOOP responds favorably to corticosteroids, the other patterns respond poorly to corticosteroids and other immunosuppressive therapy thus having a poor prognosis. NSIP pattern is the dominant histologic pattern in many of the collagen vascular diseases (myositis, scleroderma) [4]. In contrast to other collagen diseases, the UIP pattern seems to be more common in rheumatoid arthritis [7].

In the present study, we tried to identify the prognostic groups within ASS patients based on the anti-SS-A antibody positivity. We evaluated the severity, clinical characteristics and pattern of ILD among those ASS patients where anti-SS-A antibody was also present. The data were compared with other ASS patients without anti-SS-A antibody as controls.

## Patients and methods

The study population consisted of 27 myositis patients with anti-Jo-1 positivity PM ($n = 17$), DM ($n = 5$), SSc overlap ($n = 3$), RA overlap ($n = 2$) among 315 IIM patients. The patients were followed on a regular basis between 1976 and 2007 as per our institutional protocol.

Patients who fulfilled the modified Peter and Bohan criteria for IIM formed the study groups [8, 9]. Clinical data were obtained from patients' medical records. All patients underwent detailed clinical examinations to exclude malignancy and characterize the extramuscular involvement. Disease duration was considered to be the interval between the date of diagnosis of the disease and the date of the most recent follow-up visit. All patients also underwent routine laboratory examinations at diagnosis: ESR, CK, LDH with routine laboratory methods from peripheral blood. Laser nephelometry was used to detect the presence of RF and CRP (Dialab GmBH, Austria); antinuclear antibodies (ANA) were detected by indirect immunofluorescence method using Hep-2 cell culture. Antibodies directed against extractable nuclear antigen (ENA) complex: anti-SS-A, anti-SS-B, anti-Jo-1 antibodies were measured by enzyme-linked immunoassay (ELISA, HYCOR Biomedical Inc., CA, USA) method. The presence of anti-Jo-1 antibody was also confirmed by immunoblotting (Euroline-WB, Euroimmun, Lübeck, Germany).

All ASS patients underwent electromyography, muscle biopsy, chest radiography, high-resolution computer tomography (HRCT) of the lung, and pulmonary function tests. Pulmonary function tests were performed using a computer-based device (Piston, Hungary, PDT-111).

Results were expressed as percentage of predictive values based on a patient's sex, age, height and weight.

HRCT was performed with slices of 1 mm interval and scored semiquantitatively according to Kazerooni by an independent radiologist who was unaware of any clinical or physiological findings [9]. HRCT scores were compared between the two groups. Alveolar or interstitial score ≥2 was used to define lung involvement [7]. Our working hypothesis was that ILD patterns on HRCT have a good correlation with the findings of open lung biopsy and the risk of intervention exceeds the benefit [4]. Mild ILD was defined as asymptomatic pulmonary infiltrates. Moderate to severe ILD is defined by one or more of the following: significant pulmonary dysfunction, extensive radiologic findings at diagnosis and progression of disease despite glucocorticoids (0.75–1 mg/kg/day) for minimum 8 weeks) and azathioprine (1.5–2.5 mg/kg/day). The clinical course of each patient was determined based on the pulmonary function test results after therapy compared to basal results. Improvement was defined if there was more than a 15% improvement in PFT results or any improvement in radiographic images, deterioration if there was more than a 15% drop in PFT results or any worsening in radiographic images and stationary if the change did not satisfy either criteria of improvement or deterioration [10]. As per the recommendations, bronchoscopy, bronchoalveolar lavage and lung biopsy were performed in case of refractory ILD, if the disease had showed progression despite the immunosuppressive therapy or infection had been suspected.

### Therapeutic regimens

Treatment protocols we used were irrespective of the autoantibody status; in case of mild asymptomatic ILD corticosteroid therapy as first line treatment, initially 0.75–1 mg/kg daily intravenous methylprednisolone for 2–3 weeks followed by oral dosing for another 5–6 weeks and slow tapering afterward as usual in myositis therapy alone was followed. Concomitant treatment with azathioprin (1.5–2.5 mg/kg daily) or cyclosporin-A (3–4 mg/kg daily) was added for a period of 4–12 months. In case of symptomatic progressive moderate or severe ILD, the most frequently used combinations were oral methylprednisolone (0.2–0.4 mg/kg daily) with pulse cyclophosphamide therapy (750–1,000 mg/dose iv) monthly at least six times as induction therapy and cyclosporin-A or azathioprin as maintenance therapy to achieve good therapeutic response. In case of refractory, progressive ILD, the combinations mentioned earlier were given and intravenous immunoglobulin (0.5 g/kg per month) was used as a salvage therapy. Recently the use of rituximab can be considered in these cases [4, 11, 12].

### Statistics

All statistical analyses were performed with the SPSS version 15.0 software (SPSS, Chicago, IL, USA); $p$ value was set at less than 0.05. The groups were analyzed with the following tests. In case of normal distribution the independent sample $t$ test and in non-normal distribution when different samples were used the Mann–Whitney test were used to compare the means. The Chi-square test was used to compare frequencies. However, caution is needed in interpreting statistical significance given the relative small number of patients.

## Results

Twenty-seven (8.6%) ASS patients (2:25, male:female) with a mean age of 39.96 years (range 17.9–67.3) at the time of diagnosis were included in the study (Table 1). ANA was positive (titer ≥ 1:160) in 44.4% of the ASS patients and 44.4% also resulted positivity for anti-SS-A antibody. Mean disease duration (from first symptoms until present) was 46.6 (range 4–198) months. No significant differences were found in age, sex, disease duration between the two groups (Table 3). Prevalence of ILD was found to be 21% in all 315 myositis cases, however developed in 70.3% of the Jo-1 positive cases. There was no clinically significant difference in the characteristic clinical symptoms between the two groups (Table 2).

ILD was revealed at diagnosis in 52.6% of the antisynthetase cases and 30% of patients were asymptomatic at diagnosis. Normal chest radiograph has been found in 20% of patients ($n = 2$), where HRCT confirmed ILD. ILD appeared later in 47.4% of cases approximately 3.12 years (range 0.08–6 years) after the myositis diagnosis. 73.3% of SS-A negative patients developed ILD compared to 66.7% of SS-A positive patients. 54.4% of SS-A negative AS patients with ILD were asymptomatic at diagnosis, but ground-glass opacity could be revealed in four of these cases by HRCT examination (Table 3).

**Table 1** Classification of Jo-1 positive antisynthetase syndrome patients according to Peter and Bohan criteria at diagnosis

| | *N* | ILD | No ILD |
|---|---|---|---|
| Total | 27 | 19 | 8 |
| Polymyositis | 17 | 13[a] | 4 |
| Dermatomyositis | 5 | 1 | 4 |
| Overlap myositis | 5 | 5[a] | 0 |

*ILD* interstitial lung disease

[a] 2 PM, 1 OM patients died

**Table 2** Clinical characteristics of the antisynthetase syndrome patients at diagnosis based on anti-SS-A antibody positivity

| Total | Anti-Ro/SS-A negative ($n = 15$) | Anti-Ro/SS-A positive ($n = 12$) |
|---|---|---|
| Mechanic hand | 2 | 1 |
| Raynaud's phenomenon | 14 | 12 |
| Polyarthritis/arthralgia | 14 | 12 |
| Fever | 3 | 7 |
| Heliotrop rash | 2 | 2 |
| Gottron's papula | 2 | 2 |
| Proximal muscle weakness | 15 | 12 |

Mean alveolar score was 1.27 (SD: ±1.34), mean interstitial score was 2.27 (SD: ±0.91) in the SS-A negative group. However, in the SS-A positive group, there were no patients with HRCT alveolar score greater than 2, whereas the mean interstitial score was 2.75 (SD: ±2.05) ($p < 0.05$). HRCT pattern of ILD in the SS-A negative patients was found to be less coarse with more extent ground-glass opacity as can be seen in NSIP. HRCT pattern of ILD was found to be similar as can be seen in UIP in the SS-A positive cases (Table 4).

FEV1% was found to be 69.3% (SD: ±5.78) in the SS-A negative subgroup before therapy, and 80.1% (SD: ±3.77) after therapy ($p < 0.05$). FEV1% was found to be 78.46% (SD: ±5.94) in the SS-A positive subgroup and 78.87% (SD: ±3.86) after therapy. FVC was found to be 2.36 l (SD: ±0.61) in the SS-A negative subgroup before therapy and 2.83 l (SD: ±0.72) after therapy. FVC was found to be 2.3 l (SD: ±0.6) in the SS-A positive subgroup before therapy and 2.38 l (SD: ±0.72) after therapy (Figs. 1, 2).

FEV1% and FVC increased significantly after therapy in the SS-A negative subgroup ($p < 0.05$) compared to the SS-A positive subgroup (Figs. 3, 4). Overall, 72.7% of SS-A negative patients who were treated improved or remained stable on treatment compared with only 12.5% of SS-A positive patients (Table 5). Two of the SS-A positive ASS patients also received intravenous immunoglobulin therapy in addition to the previous immunosuppressive agents due to refractory, progressive ILD. Three (25%) of the SS-A positive antisynthetase patients died due to pulmonary or secondary cardiac complications; their ILD seemed to be refractory to immunosuppressive therapy, partially due to diagnostic delays, and progressive irreversible fibrosis.

**Table 3** Demographics and clinical characteristics of Jo-1 positive antisynthetase syndrome patients with ILD based on anti-SS-A antibody positivity

| Total | Anti-Ro/SS-A negative ($n = 11$) | Anti-Ro/SS-A positive ($n = 8$) | $p$ value |
|---|---|---|---|
| Mean age at diagnosis (years, mean ± SD) | 43.8 (17.9–67.3) | 35.2 (24.6–50.8) | n.s. |
| Male:female | 0:11 | 1:7 | |
| Disease duration (months) | 44.3 (4–198) | 52 (14–87) | n.s. |
| Slowly progressive pattern | 5/11 (55.5%) | 7/8 (87.5%) | <0.05 |
| Asymptomatic pattern | 6/11 (54.5%) | 1/8 (12.5%) | <0.05 |
| Dyspnea | 5/11 (55.5%) | 6/8 (75%) | <0.05 |
| Cough | 4/11 (44.4%) | 5/8 (62.5%) | <0.05 |
| Initial FVC after therapy (l) | 2.36 (±0.61 SD)<br>2.83 (±0.72 SD) | 2.30 (±0.6 SD)<br>2.38 (±0.72 SD) | n.s.<br>n.s. |
| Initial FEV1 after therapy (%) | 69.3 (±5.78 SD)<br>80.1 (±3.77 SD) | 78.46 (±5.94 SD)<br>78.87 (±3.86 SD) | <0.05<br>n.s. |

Basic characteristics of the two subgroups of patients. This table shows all patients with overlap cases included

*ILD* interstitial lung disease, *ASS* antisynthetase syndrome, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s

**Table 4** Interstitial and alveolar HRCT scores in the asymptomatic and symptomatic ILD cases at diagnosis

| HRCT findings at diagnosis | Anti-Ro/SS-A negative ($n = 11$) | | Anti-Ro/SS-A positive ($n = 8$) [symptomatic ($n = 7$)] |
|---|---|---|---|
| | Symptomatic ($N = 5$) | Asymptomatic ($N = 6$) | |
| HRCT alveolar score ≥ 2 | 2 | 4 | 0 |
| HRCT interstitial score ≥ 2 | 5 | 5 | 5 |
| HRCT mean alveolar score | 1.2 | 1.3 | 0 |
| HRCT mean interstitial score | 2.4 | 2.16 | 2.75 |

*HRCT* high-resolution computer tomography

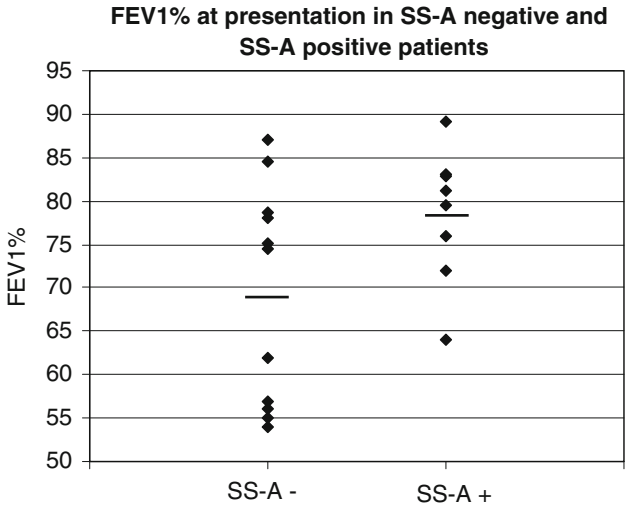


**Fig. 1** FEV1% at presentation in the SS-A negative and positive antisynthetase syndrome patients. *FEV1%* forced expiratory volume in 1 s

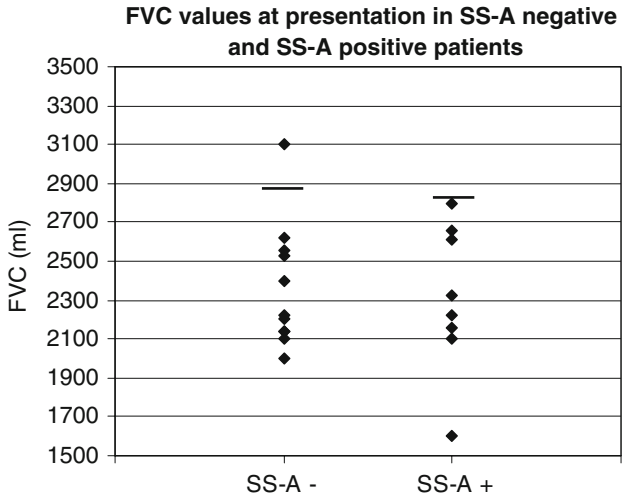


**Fig. 2** FVC values at presentation in the SS-A negative and positive patients. *FVC* forced vital capacity

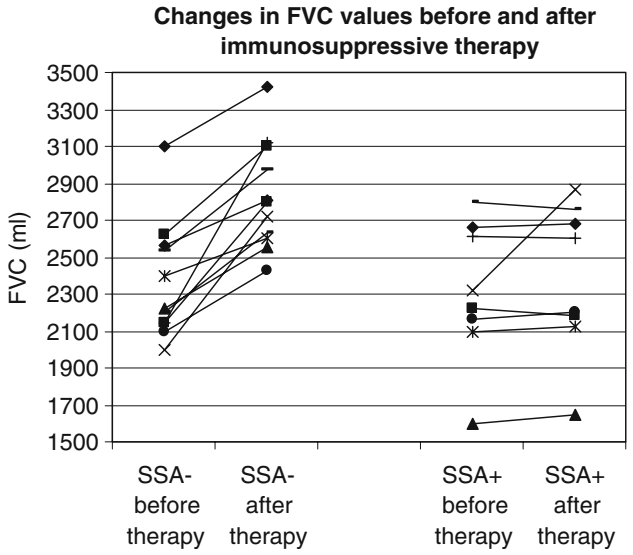


**Fig. 3** Changes in FVC values before and after the immunosuppressive therapy. *FVC* forced vital capacity

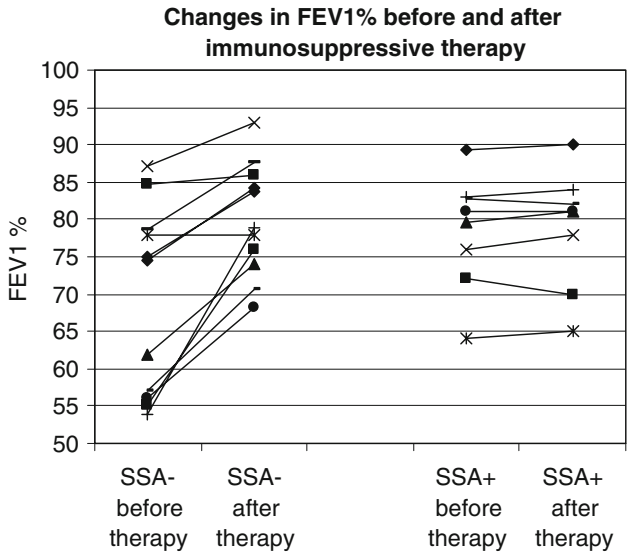


**Fig. 4** Changes in FEV1% before and after the immunosuppressive therapy. *FEV1%* forced expiratory volume in 1 s

## Discussion

The challenge in treating IIM is to identify those patients who require early aggressive treatment. Our study highlights one possible autoantibody pattern to predict this. We reported a clinical study of 19 ASS cases among 315 myositis patients (6.1%) who had been diagnosed as having ILD. Prevalence of ILD was found to be 70.4%, these findings are similar to those previously reported, where the frequency of ILD in patients with anti-Jo-1 antibody is more than 70% [4, 5, 13]. 52.6% of ILD cases were asymptomatic at the myositis diagnosis. This is higher than reported by Fathi et al. [4] where 27% of the patients with myositis with ILD were asymptomatic at diagnosis. The possible difference may be the extended referral system and earlier diagnosis of IIM in our area. Normal chest radiograph was found to be in 20% of the patients with HRCT proven ILD. This is higher than that reported by Fathi et al. (10%) [4]. This verifies our protocol where all patients with ASS are regularly followed up by HRCT scans irrespectively of clinical symptoms. Follow-up assessment including pulmonary function tests, chest radiography and HRCT is required after 3 months to evaluate the therapeutic response [4].

The ASS group without anti-SS-A antibody had a more frequent association with alveolitis, presented with

**Table 5** Clinical course of pulmonary involvement in antisynthetase syndrome patients based on anti-SS-A antibody positivity

| | ILD clinical course (no. of patients) | Remission | No change | Progressive | Death | Cause of death |
|---|---|---|---|---|---|---|
| SS-A negative | Asymptomatic ($n = 6$) | 4 | 2 | – | 0 | _ |
| SS-A negative | Slowly progressive ($n = 5$) | 1 | 1 | 3 | 0 | _ |
| SS-A positive | Asymptomatic ($n = 1$) | – | – | 1 | 0 | _ |
| SS-A positive | Slowly progressive ($n = 7$) | 1 | – | 6 | 3 | ILD, with pulmonary infection, heart failure |

Response to adequate therapy is indicated in the table

*ILD* interstitial lung disease

increased alveolar scores, and half of the patients were asymptomatic at diagnosis (54.5%), and responded well to immunosuppressive therapy as used in the treatment of myositis alone. This is due to the fact that alveolitis represents active inflammatory process which can be well controlled with immunosuppressive therapy. ASS patients with coexistent anti-SS-A antibodies tended to have a more severe form of ILD represented by the different HRCT pattern and increased interstitial scores at diagnosis. Clinical outcome, radiology and treatment response have all been quite different in the subset of individuals with SS-A positivity. Response to therapy was significantly better if anti-SS-A antibody was not present. These findings are supported by La Corte et al. [1] who studied 21 antisynthetase and 48 patients with classical dermato- and polymyositis. ASS patients with anti-SS-A antibody seemed to be predisposed to the development of more severe ILD. We conclude that immunosuppressive therapy was especially useful in acute phase of ILD and we experienced less response to therapy when the patient's pulmonary fibrosis was more coarse due to more aggressive definite fibrotic changes at diagnosis as can be seen in UIP.

In summary, our study has shown that antisynthetase patients without SS-A antibody carry a significantly better prognosis than antisynthetase patients with anti-SS-A antibody. Thus, the coexistence of anti-Jo-1 and anti-SS-A positivity could serve as a good predictor to identify candidate patients for severe progressive ILD and early aggressive therapy.

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**Conflict of interest statement** No conflict of interest has been declared by the authors.

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